REMARKS

Claims Status

Claims 1 and 3-30 are pending in the subject application.

Lack of Unity

The Examiner alleges that the subject application contains inventions or groups of inventions that are not so linked as to form a single general inventive concept under PCT Rule 13.1. Thus, the Examiner requires restriction and election of a single invention from Examiner's Groups 1 to 42 (see Office Action, pages 2-6).

The Examiner states that under the PCT's unity of invention, special technical features are defined as those that identify a contribution that each of the claimed inventions, considered as a whole, makes over the prior art. The Examiner alleges that the inventions listed as Groups 1-42[1] do not relate to a single general inventive concept because the claims lack the same or corresponding technical features in view of Khisti et al. (2000). The Examiner alleges that Khisti et al. disclose the use of fluoxetine (an SSRI) and bicuculline (a GABA antagonist) as effective in a mouse model of depression, and as such, further alleges that the combination was effective at reducing immobility time. The Examiner also alleges that Khisti et al. administer the combination and treat depression with same (see, e.g., Office Action, page 6).

The Examiner further alleges that Groups 1-2 are drawn to various treatments using different SSRIs and different GABA receptor antagonists, and requires election of a single SSRI and a single GABA antagonist. The Examiner alleges that the drugs do not share a special technical feature with one another and are therefore further restricted. The Examiner alleges that this requirement is *not* an election of species (see, e.g., Office Action pp. 6-7).

[1] In the Examiner's allegation, Groups 1-55 are identified, though only 42 groups are provided. Consequently, Applicants correct what they believe is a typographical error by the Examiner.

Finally, the Examiner has acknowledged that rejoinder, in accordance with the provisions of MPEP 821.04, is available as a matter of right to Applicants upon allowance of the elected product claims (see, e.g., Office Action, pp. 7-8).

In response to this Restriction Requirement, Applicants elect, with traverse, the invention of Group 22, i.e., claims 12-21, drawn to a pharmaceutical composition comprising a serotonin reuptake inhibitor (SRI) compound and a $GABA_B$ receptor antagonist, inverse agonist or partial agonist compound.

Applicants traverse the Examiner's allegation of lack of unity under PCT Rule 13.1 because the inventions of Groups 1-42 are unified by the technical feature of a combination of a **$GABA_B$** receptor antagonist, inverse agonist or partial agonist and a SRI. Applicants maintain that the combination is not disclosed in Khisti et al., and therefore the technical relationship among the claims as a whole is Applicants' contribution over the prior art.

Single General Inventive Concept

PCT Rule 13.1 recites in part: "The international application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ...."

Applicants maintain that the single inventive concept of the subject application is the combination therapy of a **$GABA_B$** receptor antagonist, inverse agonist or partial agonist and a serotonin reuptake inhibitor (SRI).

Contribution Over the Prior Art

PCT Rule 13.2 recites:

> Where a group of inventions is claimed in one and the same international application, the requirement of unity of invention referred to in Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features

that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

The Examiner cited Khisti et al. as prior art in asserting a lack of unity rejection, as previously described above (see also the Office Action at page 6, Section 2). However, the Examiner is respectfully mistaken.

Khisti et al. describes the investigation of an endogenous neurosteroid metabolite called 3α-hydroxy-5α-pregnan-20-one, commonly known as 3α-5α-THP, and its antidepressant-like effects (see, e.g., p. 137, Introduction, lines 1-10). 3α-5α-THP is known as a **$GABA_A$** receptor activating (agonist) compound (see, e.g., p. 137, Introduction, column 1, line 4 through column 2, line 10).

Khisti et al. further describe the administration of **$GABA_A$** receptor-specific compounds, such as muscimol (agonist) and bicuculline (antagonist) in combination with the SRIs, fluoxetine or imipramine (see, e.g., p. 139, section 2.5, and Table 3). Yet Khisti et al. do not describe any **$GABA_B$** receptor antagonist, inverse agonist or partial agonist, *much less* a **$GABA_B$** receptor antagonist, inverse agonist or partial agonist *in combination with* an SRI.

Clearly, then, Khisti et al. does not establish that this special technical feature of the present application is known; thus, this technical feature is a contribution over Khisti et al. and the present invention has unity.

Moreover, Applicants unexpectedly discovered that co-administration of a **$GABA_B$** receptor antagonist, inverse agonist or partial agonist *and* an SRI, in contrast to the administration of one drug alone, significantly *elevates* serotonin (5-HT) levels in the brain, as measured by microdialysis (see, e.g., Figures 2-6 of the present application.) This result contrasts with the co-administration of a **$GABA_A$** receptor antagonist and SRI, where the combination *fails to further increase* the 5-HT levels in the brain when compared to SRI alone (see, e.g., Figure 1 of the present application). Yet Khisti et al. neither teaches nor suggests that a **$GABA_B$** receptor antagonist, inverse agonist or partial agonist in combination with an SRI would enhance the 5-HT levels in the brain. Nor does Khisti et al. teach that the claimed combination would be useful

for the treatment of 5-HT related disorders. Therefore, Applicants' claims, in view of the description, make a contribution over Khisti et al.

Accordingly, the restriction of Groups 1-42 is not proper because the prior art does not teach the combination of a **$GABA_B$** receptor antagonist, inverse agonist or partial agonist and an SRI.

Markush Alternatives

Further, PCT Rule 13.3 recites:

> The determination whether a group of inventions is so linked as to form a single general inventive concept shall be made ***without*** regard to whether the inventions are claimed in separate claims or as alternatives within a single claim. (Emphasis added.)

Additionally, unity of invention needs to be considered in relation to the independent claims and not the dependent claims. (See MPEP, Appendix AI, ANNEX B, §(c)(i).)

Accordingly, the restriction of Groups 1-42 is not proper because the Examiner has focused Groups 1-42 on the independent claims and the dependent claims.

International Preliminary Examination Report (IPER)

Also, it is respectfully brought to the Examiner's attention that the decision with respect to unity of invention rests with the International Searching Authority or the International Preliminary Examining Authority (see, e.g., §10.05 of Chapter 10, Unity of Invention, PCT Search and Preliminary Examination Guidelines (2004), p. 75.)

Here, the International Preliminary Examining Authority did not find a lack of unity of invention for PCT/DK03/00412, the International Application on which the present [national stage] application is based (see, e.g., the attached May 28, 2004 IPER.)

The International Preliminary Examining Authority's decision, therefore, further supports Applicants' position that the restriction of Groups 1-42 is improper.

Conclusion

For the foregoing reasons, Applicants' traverse the Examiner's requirement for restriction under the PCT Rules and respectfully request that the restriction be withdrawn.

If a telephone interview would be of assistance in advancing prosecution of the above-identified application, Applicant's invite the Examiner to telephone undersigned at the number provided below.

As previously stated, the fee for a two months extension is submitted herewith. Authorization is hereby given to charge any additional fee(s), or credit any overpayment, to Deposit Account No. 50-3201.

Respectfully submitted,

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
411 WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/DK 03/00412	19.06.2003	20.06.2002

International Patent Classification (IPC) or both national classification and IPC

A61K31/662

Applicant

H. LUNDBECK A/S et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15.01.2004	28.05.2004

Name and mailing address of the international preliminary examining authority:

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Authorized Officer

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK 03/00412

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-27 as originally filed

Claims, Numbers

1-25 as originally filed

Drawings, Sheets

1/6-6/6 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 22-25

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 22-25

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-21
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-21
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-21
	No:	Claims	

2. Citations and explanations

see separate sheet

SECTION V:

Document WO 99 37303 describes the combination of a $GABA_A$ α 2/3 agonist with a selective serotonin reuptake inhibitor.

The subject-matter of the claims differs therefrom in that the serotonin reuptake inhibitor is combined with a $GABA_B$ receptor antagonist, which was not obvious for the person skilled in the art.

Therefore the subject-matter of claims 1 to 21 involves an inventive step.